UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/857,719	12/03/2001	Ryuichi Morishita	6235-59216	9622

7590 02/12/2003

Klarquist Sparkman Campbell Leigh & Whinston, LLP
One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, OR 97204

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/857,719	MORISHITA ET AL.
	Examiner	Art Unit
	Q. Janice Li	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 26-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 26-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Claims 1-18 and 26-35 are pending in the application and under current examination.

Priority

This application is a 371 of PCT/JP00/06947 and claims the benefit of priority to JP 11/288532, filed 8/10/1999.

Specification

The disclosure is objected to because of the following informalities:

The Brief description of the drawings does not match figure 1, wherein the graph shows the comparison of groups between a control and a HGF-treated group, but the description indicates it should be a showing of luciferase activity (without HGF) in guinea pigs having cardiomyopathy.

The Preliminary amendment requested insertion of a paragraph starting with "WE CLAIM" on page 11, however, page 11 contains the text of the specification, and it is improper to insert the claims there. The original page for claims starts at page 13.

Appropriate clarification is required.

Claim Objections

Claims 4, 5, and 27 are objected to because they fail to further limit a previous claim from which they depend (claims 1-3). Claims 1-3 are drawn to a therapeutic agent, whereas claims 4, 5, and 27 recite limitations for a method of administering an agent. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for intramuscular or intracoronary administration of a nucleic acid molecule encoding HGF into the cardiac muscle of a mammal, does not reasonably provide enablement for administration of *any* type of nucleic molecule encoding HGF or *any* polypeptide into the cardiac muscle of a mammal by *any* route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited

to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are drawn to administration of a nucleic acid molecule encoding HGF into the cardiac muscle of a mammal by any route of administration or injection, such as intradermal, intravenous, and intraperitoneal injection, and using any nucleic acid molecule. Given the broadest reasonable interpretation, the claims read on a gene therapy method for treating myocardiopathy in any mammal, thus, would be evaluated by that standard. The specification contemplates any means of administration using any viral or non-viral vectors (see particularly sections A and B). The specification teaches direct injection of HVJ-liposome comprising the nucleic acid encoding HGF into the abdominal lateral cardiac muscle of the heart under the usage of echocardiogram, wherein the cardiac capillary vessel density and cardiac bloodstream are increased in the HGF treated group compared to the controls. However, the specification fails to teach whether the recited nucleic acid molecule would reach the cardiac muscle of the mammal using any viral or non-viral vectors by any route of administration and the delivered nucleic acid would reach cardiac muscle in a significant amount such that a therapeutic angiogenesis in cardiac tissue would achieved, thus, fails to support the full scope of the claims.

Claims 1-10, drawn to a therapeutic agent, are rejected under this provision because the intended use limitations of the claims are drawn to a particular use of the claimed method. According to MPEP, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c). Particularly, claims 8 and 9 are drawn to any agent, not limiting to HGF, while the specification fails to teach a therapeutic effect for any agent other than HGF.

The types of the vectors and the route of administration are relevant for enabling the claimed invention because each type of virus has different tissue tropism and efficiency of transducing various types of cells. *Robbins et al* (Pharmcol Ther 1998;80:35-47) teach that each type of vector system has its unique advantages and limitations, "RETROVIAL VECTORS CAN PERMANENTLY INTEGRATE INTO THE GENOME OF THE INFECTED CELL, BUT REQUIRE MITOTIC CELL DIVISION FOR TRANSDUCTION. ADENOVIRAL VECTORS CAN EFFICIENTLY DELIVER GENES TO A WIDE VARIETY OF DIVIDING AND NONDIVIDING CELL TYPES, BUT IMMUNE ELIMINATION OF INFECTED CELLS OFTEN LIMITS GENE EXPRESSION IN VIVO. HERPES SIMPLEX VIRUS CAN DELIVER LARGE AMOUNTS OF EXOGENOUS DNA; HOWEVER, CYTOTOXICITY AND MAINTENANCE OF TRANSGENE EXPRESSION REMAIN AS OBSTACLES. AAV ALSO INFECTS MANY NONDIVIDING AND DIVIDING CELL TYPES, BUT HAS LIMITED DNA CAPACITY" (abstract). *Robbins et al* go on to teach that non-viral vectors such as naked DNA and liposomes are inefficient in gene transfer to cell nucleus (Section 2, page 36). *Miller et al* (1995, FASEB J., Vol. 9, pages 190-199), acknowledge various vector system available in the art, then teach, "NO SINGLE DELIVERY SYSTEM IS LIKELY TO BE UNIVERSALLY APPROPRIATE, FOR

INSTANCE, THE REQUIREMENTS OF GENE THERAPY FOR CYSTIC FIBROSIS ARE GREATLY DIFFERENT FROM THOSE OF CANCER" (1st paragraph, page 190). "ONCE AGAIN, TARGETING AT THE LEVEL OF THE VECTOR HAS NOT YET BEEN PARTICULARLY WELL DEVELOPED; HENCE, LIPOSOME OR VIRAL-MEDIATED DELIVERY OF THE CFTR GENE TO AIRWAY EPITHELIAL CELLS OF CF PATIENTS HAS RELIED LARGELY ON THE LOCALIZED DELIVERY OF THE VECTORS DIRECTLY TO THE AFFECTED TISSUES" (1st paragraph, page 198). Delivery of nucleic acids to cardiac tissue using routes other than direct myocardiac injection or intracoronary route would require vector targeting. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). For example, the cardiac muscle cells are not in active mitotic division, accordingly, it may be inefficient in transducing cardiac muscle by retroviral vectors. Adenoviral vectors and Sendai viral vectors (the preferred embodiment in the instant claims) have a natural tropism to respiratory epithelial cells, they may not efficient in targeting cardiac tissue. Since the specification fails to teach any targeting mechanism for the encompassed vectors, thus, these vectors would not be expect to reach the cardiac muscle in a significant amount. *Robbins et al* teach regarding gene therapy for muscle diseases such as Duchenne muscular dystrophy (DMD), "ALTHOUGH BOTH THE DEFECTIVE GENE IN THE DISEASE AND THE APPROPRIATE TARGET CELLS FOR THERAPY ARE KNOWN, SUCCESSFUL APPLICATION OF GENE THERAPY TO THE TREATMENT OF DMD IS HINDERED BY THE

GREAT AMOUNT OF MUSCLE TISSUE TO BE TARGETED. MOREOVER, THE BASAL LAMINA IN MUSCLE APPARENTLY PREVENTS EFFECTIVE INFECTION OF THE MYOBLASTS BY CURRENT VIRAL VECTORS" (Section 5.3, page 44). The specification fails to teach how to overcome the aforementioned difficulties in the art. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* gene targeting at therapeutic levels, in particular for the treatment of any and all myocardiopathy, the lack of direction or guidance provided by the specification, and the breadth of the claims directed to the use of numerous nucleic acid molecules by any route of administration, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-18, and 26-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-18 and 26-35 are vague and indefinite because of the claim recitation, "non-invasive". The specification fails to define the term, it is unclear what means of administration is considered as "non-invasive", and thus the metes and bounds of the claims are unclear. Further, claim 11 encompasses any route of injection, such as direct injection to cardiac muscle (claims 32, 34, 35), an injection to beating cardiac muscle

would be considered as "non-invasive administration". Claim 33 encompasses administration using a catheter, thus, intravascular injections such as intracoronary injection would meet claim limitation.

Claims 4, 5, and 27 are vague and indefinite because they recite means of administering the agent; it is unclear whether applicants intend to claim a method or an agent.

Claims 11 and 16 are incomplete. The claims provide a method for treating a disorder, however, it does not recite any positive step which clearly relates back to the preamble, it is unclear how administration of the nucleic acid relates to the treatment of myocardiopathy and whether the goal of the method has been resolved.

Claim 33 recites the limitation "the affected tissue". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1-12, 15, 26-29, 32, 34, and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by *Morishita et al* (US Patent No. 6,248,722).

Claims 1-10, and 26-28 are drawn to a composition comprising (preferably) at least 10 μg of nucleic acid molecule encoding a hepatocyte growth factor (HGF) in a pharmaceutical suitable carrier for injection into cardiac muscle, wherein said molecule comprises a Sendai virus-liposome (HVJ-liposome).

Morishita et al teach a composition comprising a nucleic acid encoding HGF, wherein the nucleic acid is encapsulated by a liposome, and the membrane of which may be further fused to attenuated Sendai virus particles (HVJ-liposome, example 1). *Morishita et al* go on to teach that the HGF-HVJ-liposome could be used as a medicament for the treatment or prevention of human disease (column 4, lines 17-22), and be prepared in various pharmaceutical forms for *in vivo* administration (column 6, lines 29-47), and the preferred dosing range is from 1 μg to 10 mg HGF (column 6, lines 50-54).

Claims 11, 12, 15, 29, 32, 34, and 35 are drawn to a method for treating myocardiopathy, comprising administering the HGF-HVJ-liposome into the cardiac muscle of a mammal, preferably directly to the affected cardiac muscle.

Morishita et al teach a method comprising administering the HGF-HVJ-liposome intramuscularly to a subject (claims 1-3), wherein the subject may have a myocardial disease (column 4, lines 43-44), wherein the HGF-HVJ-liposome could be delivered directly to the objective organ of diseases (column 6, lines 5-14), such as into the muscle of the heart (example 8).

Accordingly, *Morishita et al* anticipate instant claims.

Please note that in this and the following rejections, intended use limitations for the product claims bear little weight on the determination of novelty of the invention. The claim limitation "used in a method for noninvasive administration comprises echocardiography guided administration" or "administered once a week" does not carry patentable weight in the determination of anticipation for the claimed products. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claims 1-12, 15, 26-29, 32, 34, and 35 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 09/660,522 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

The reference application qualifies as prior art under this provision because it has a different inventive entity and no showing of common ownership between the instant application and the cited application at the time of Applicant's invention.

The cited copending application is a continuation of US patent 6,248,722, therefore the reasoning presented in the immediate preceding rejection applies to the cited copending application because the disclosure of the cited copending application and the '722 patent is the same.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Claims 1-10, and 26-28 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 09/856,374 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

The reference application qualifies as prior art under this provision because it has a different inventive entity and no showing of common ownership between the instant application and the cited application at the time of Applicant's invention.

The cited application discloses an agent comprising the HGF gene as active ingredient, and the preferred embodiment is in the form of HVJ-liposome, comprising 20 μg of the nucleic acid molecule (>10 μg, Example I, particularly, 2nd paragraph, page 27).

Accordingly, the co-pending application anticipates instant claims.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Claims 1-12, 15, 26-29, 32, 34, and 35 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

US. Patent No. 6,248,722 has a different inventive entity with the instant application; however, the cited patent anticipates the claimed subject matter. Further clarification is required with regard to the inventorship.

Claims 1-12, 15, 26-29, 32, 34, and 35 are provisionally rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

U.S. Patent Application Serial No: 09/660,522 has a different inventive entity with the instant application; however, the claimed subject matter is obvious over the cited application. Further clarification is required with regard to the inventorship.

Claims 1-10, and 26-28 are provisionally rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

U.S. Patent Application Serial No: 09/856,374 has a different inventive entity with the instant application; however, the claimed subject matter is anticipated by the cited application. Further clarification is required with regard to the inventorship.

Claims 1-12, 15, 26-29, 32, 34, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by *WO 97/07824.*

Claims 1-10, and 26-28 are drawn to a composition comprising (preferably) at least 10 μg of nucleic acid molecule encoding a hepatocyte growth factor (HGF) in a pharmaceutical suitable carrier for injection into cardiac muscle, wherein said molecule comprises a Sendai virus-liposome (HVJ-liposome).

WO 97/07824 teaches a composition comprising a nucleic acid encoding HGF, and further comprising liposome-Sendai virus particles (HVJ-liposome, example 1, section bridging pages 12-13). *WO 97/07824* goes on to teach that the HGF-HVJ-liposome could be used as a medication in human diseases (2nd paragraph, page 6), prepared in various pharmaceutical forms for *in vivo* administration (2nd paragraph, page 9), and the preferred dosing range is from 1 μg-10 mg HGF (3rd paragraph, page 9).

Claims 11, 12, 15, 29, 32, 34, and 35 are drawn to a method for treating myocardiopathy, comprising administering the HGF-HVJ-liposome into the cardiac muscle of a mammal, preferably directly to the affected cardiac muscle.

WO 97/07824 teaches a method comprising administering the HGF-HVJ-liposome intramuscularly to the heart of a subject (example 8), wherein the subject may have a myocardial disease (2nd paragraph, page 6), wherein the HGF-HVJ-liposome could be delivered directly to the objective organ of diseases (lines 20-24).

Accordingly, *WO 97/07824* anticipates instant claims.

Claims 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by *Hammer et al* (US 5,792,453).

The claims are drawn to a therapeutic agent comprising a nucleic acid molecule encoding a polypeptide, wherein the intended use for the agent is for non-invasive administration to an affected part of a tissue using an echocardiograph, preferably the cardiac muscle.

Hammer et al teach a nucleic acid encoding FGF-5 (example 1) for gene transfer by a catheter in myocardium (column 5, line 19) guided by echocardiography (figures 2-4). Thus, *Hammer et al* anticipate the instant claims.

Claims 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by *Esakof et al* (Hum Gene Ther Sept 1999;10:2307-14, IDS).

Esakof et al teach a nucleic acid encoding a polypeptide (vascular endothelial growth factor) for myocardial tissue gene delivery. Thus, *Esakof et al* anticipate the instant claims.

Claims 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by *Maurice et al* (J Clin Invest Jul 1999;104:21-9).

Maurice et al teach a nucleic acid (adenoviral vector) encoding a polypeptide (human beta2-adrenergic receptor) for myocardial tissue gene delivery. Thus, *Maurice et al* anticipate the instant claims.

Claims 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by *Aoki et al* (Circulation 1998;98:I321, IDS).

Aoki et al teach a nucleic acid encoding HGF for gene transfer in myocardium. Thus, *Aoki et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-14, 16-18, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over *WO 97/07824,* in view of *Esakof et al* (Hum Gene Ther 1999 Sept;10:2307-14, IDS).

These claims are further drawn to using an echocardiography guiding the administration of the HGF-HVJ-liposome at a repeated regimen, i.e. once a week for 8 weeks. *WO 97/07824* fails to teach these limitations. However, before the effective filing date of the instant application, *Esakof et al* teach using echocardiography (TEE or MPTEE) to guide the direct myocardial vector transfer (a nucleic acid encoding and expressing VEGF), and teach the advantage of using TEE in cardiovascular procedures, particularly for multiple intramuscular injections, "MPTEE WAS USEFUL IN THE PRESENT PROTOCOL FOR DOCUMENTING A LACK OF ACUTE ADVERSE CONSEQUENCES ASSOCIATED WITH MULTIPLE INTRAMUSCULAR INJECTIONS OF RELATIVELY LARGE FLUID VOLUMES INTO THE MYOCARDIUM OF PATIENTS" (paragraph bridging pages 2312-3).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *WO 97/07824* and *Esakof et al* by simply using TEE guidance for single or multiple administration of the HGF-HVJ-liposome with a reasonable expectation of success. The ordinary skilled artisan

would have been motivated to modify the method because it provides imaging aid for surgical procedures and minimizes the tissue injury during gene delivery. As to the specific dosing regimen, it is within the knowledge of the skilled in the art to determine appropriate dose and dosing frequency according to the disease to be treated and the patient's condition as taught by both *Esakof et al* and *WO 97/07824* (3rd paragraph, page 9). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 11-14, 16-18, 30, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over *WO 97/07824, Esakof et al* (Hum Gene Ther 1999 Sept;10:2307-14) as applied to 11-14, 16-18, 30, and 31 above, and further in view of *Maurice et al* (J Clin Invest 1999;104:21-9).

Claim 33 is drawn to administration of the HGF-HVJ-liposome through a catheter. *WO 97/07824* fails to teach the limitation and *Esakof et al* only implicitly teach the limitation. However, before the effective filing date of the instant application, *Maurice et al* teach delivering a nucleic acid encoding a gene of interest to myocardial tissue through a catheter via introcoronary route, and observed multichamber myocardial expression of the nucleic acid. *Esakof et al* teach, "IN THE INTRAOPERATIVE SETTING, TEE HAS PROVED INVALUABLE FOR CONFIRMING THE PLACEMENT OF CATHETERS NEEDED FOR MINIMALLY INVASIVE, PORT-ACCESS CARDIAC SURGERY" (paragraph bridging pages 2312-3).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *WO 97/07824 and Esakof*

et al, by simply combining TEE and intracoronary catheter in the delivery of the HGF-HVJ-liposome with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because it provides imaging aid for surgical procedures, and the delivered nucleic acid could reach broader areas of the heart. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 11-13, 16-18, 30, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over *WO 97/07824,* in view of *Hammer et al* (US 5,792,453).

These claims are drawn to using an echocardiography guiding the administration of the HGF-HVJ-liposome to the cardiac muscle via a catheter. *WO 97/07824* fails to teach these limitations. However, before the effective filing date of the instant application, *Hammer et al* teach using echocardiography (e.g. figure 4) to guide the direct myocardial gene transfer (a nucleic acid encoding and expressing an angiogenic peptide) by a catheter (paragraph bridging columns 3 and 4).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *WO 97/07824*, by simply using echocardiography guidance for administration of the HGF-HVJ-liposome by a catheter with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because it provides imaging aid for determining the location of the catheter. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11, 12, 15, 29, 32, 34, and 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-6 of U.S. Patent No. 6,248,722.

The reference patent qualifies as prior art under this provision because there is at least one common inventor and no common assignee between the instant application and the cited patent.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and the claims 1, 2, 4-6 of the cited patent are each drawn to a method for treating a disease comprising administration of a therapeutically effective amount of a nucleic acid molecule encoding HGF to a subject, wherein the nucleic acid molecule comprises an attenuated Sendai virus fused with the membrane of a liposome, wherein the subject has a cardiovascular disease, wherein

the administration is via intramuscular injection, wherein the nucleic acid molecule is a medicament for the treatment or prevention of human disease.

The processes of the present application and the cited patent differ one from the other in that the claims of the cited patent do not particularly recite administering the nucleic acid encoding HGF into the *cardiac* muscle or naming a cardiac disease, such as angina pectoris, and cardiomyopathy. However, they are fully disclosed in the specification of the cited patent as the preferred embodiment. For example, the cited patent teaches that HGF gene could be introduced in vivo for the treatment and prevention of diseases, such as myocardial infarction, myocardia insufficiency, etc. (column 4, lines 34-44). In example 8 of the cited patent, the HVJ-liposome was introduced to the heart muscle by direct injection.

Accordingly, the claimed processes in the present application and the cited patent are obvious variants. Therefore, the inventions as claimed are co-extensive.

Claims 11, 12, 15, 29, 32, and 33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7 and 8 of copending Application No. 09/660,522, in view of *Maurice et al* (J Clin Invest 1999;104:21-9).

The reference application qualifies as prior art under this provision because it has a different inventive entity and no showing of common ownership between the instant application and the cited application at the time of Applicant's invention.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the present application encompass the claims 7

and 8 of the cited application, and they are each drawn to a method for treating a cardiovascular disease comprising administration of a therapeutically effective amount of a nucleic acid molecule (or expression vector) encoding HGF gene to the cardiac tissue (muscle) in a subject, wherein the nucleic acid molecule is encapsulated in a liposome, the membrane of which may be fused to an attenuated Sendai virus, wherein the subject has a cardiovascular disease.

The processes of the present application and the cited patent differ one from the other in that the claims of the present application do not particularly recite administering the nucleic acid encoding HGF *intracoronarily*. However, before the effective filing date of the instant application, *Maurice et al* teach delivering a nucleic acid encoding a gene of interest to myocardial tissue using a catheter via introcoronary route, and the nucleic acid diffusely expressed in multi-chamber myocardial tissue. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by the cited copending application and *Maurice et al* by simply delivering the HGF-HVJ-Liposome via intracoronary route to the cardiac muscle with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because the nucleic acid could reach multi-chambers of the heart by the intracoronary route. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Moreover, considerable overlap is also noted in the present claims and claims of the cited application. For example, intra-coronary administration (claim 7 of the cited

application) would require the use of a catheter, thus claim 33 of the instant application encompasses claim 7 of the copending application.

Accordingly, the claimed processes in the co-pending and the present application are obvious variants. Therefore, the inventions as claimed are co-extensive.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 11, 12, 15, 29, 32, and 33 are directed to an invention not patentably distinct from claims 7 and 8 of commonly assigned copending application 09/660,522, specifically for reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending application 09/660,522, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Claims 1-10, and 26-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent Application Serial No: 09/856,374.

Claims 1-10 and 26-28 are directed to an invention not patentably distinct from claims 1-11 of commonly assigned copending application 09/856,374. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and claims 1-11 of the cited application are each drawn to an agent comprising the HGF gene as an active ingredient.

The claims of the present application and the cited patent differ one from the other in that the cited copending application does not particularly recite the dosage of the nucleic acid molecule, however, the specification teaches the proper dosing regimen, e.g. working Example I uses 20 μg of HGF plasmid, which is more than 10 μg. The claims of the present application and the cited patent further differ one from the other in that the preamble of the claims and dependent claims are drawn to different means of using the agent in different types of diseases. However, the novelty of the agent is determined by the chemical structure of the HGF gene and nucleic acids that expressing the HGF, not the intended use.

Accordingly, the inventions as claimed are co-extensive.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

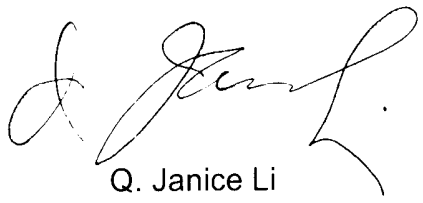
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Patent Examiner
Art Unit 1632

QL
February 10, 2003